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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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25032	7590	07/25/2006	EXAMINER	
MIRUS CORPORATION 505 SOUTH ROSA RD MADISON, WI 53719			GIBBS, TERRA C	
			ART UNIT	PAPER NUMBER
			1635	
DATE MAILED: 07/25/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/007,459

Applicant(s)

LEWIS ET AL.

Examiner

Terra C. Gibbs

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 May 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 11 and 13-18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 11 and 13-18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission mailed on May 15, 2006 has been entered.

Claims 11 and 13 have been amended.

Claims 11 and 13-18 are pending in the instant application.

Claims 11 and 13-18 have been examined on the merits.

Response to Arguments

Applicants Amendment and Response mailed May 15, 2006 have been considered. Rejections and/or objections not reiterated from the previous office action mailed February 22, 2006 are hereby withdrawn. Any arguments addressing said rejections and/or objections are moot. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Response to Amendment

Applicant's Terminal Disclaimer filed October 25, 2005 to claim priority to prior U.S. Patent No. 6,379,966 has been considered by the Examiner and has been approved. However, Applicant's Terminal Disclaimer filed October 25, 2005 to pending second application 10/012,804 has not been considered by the Examiner because the fees were not authorized. Accordingly, Applicant's Terminal Disclaimer filed October 25, 2005 has not been approved.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11 and 13-17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 7 of copending Application No. 10/186,757. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of the copending Application are drawn to patentably indistinguishable subject matter. For example, the instant claims are drawn to a process for inhibiting the expression of a gene in a cell in a target tissue in a mammal comprising mixing a double stranded RNA and a polymer or non-viral vector to form a complex wherein the zeta potential of the complex is less negative than the zeta potential of the double strand RNA alone and inserting the complex into an efferent or afferent mammalian vessel *in vivo* thereby increasing permeability of the vessels within the target tissue and delivering the double strand RNA to the cell, wherein the double strand RNA inhibits expression of the gene. The claims of copending Application No. 10/186,757 are drawn to a process for delivering an siRNA to a mammalian cell comprising mixing the siRNA and at least a compound to form a complex wherein the zeta potential of the complex is less negative than the zeta potential of the siRNA alone and inserting the complex into an afferent or efferent vessel to increase permeability of the vessel wherein expression of the gene is inhibited. It is noted that the difference between the instant claims and the claims of the copending Application is the recitation of using a dsRNA versus an siRNA, respectively. However, siRNA is a species of the broader genus of dsRNA. In this regard, the instant claims fully encompass the claims of copending Application No. 10/186,757. Furthermore, one of ordinary skill in the art, in examining the full disclosure

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of the instant claims to better practice the invention, would be appraised of the fact that siRNA are dsRNA.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 recites the limitation, "wherein the solution" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 17 from which claim 18 depends recites the term "fluid".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 11, 13, 14, 15, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Sioud et al. (Nature Biotechnology, 1998 Vol. 16:556-561).

Claim 11 is drawn to a process for inhibiting the expression of a gene in a cell in a target tissue in a mammal comprising mixing a double stranded RNA and a polymer or non-viral vector to form a complex wherein the zeta potential of the complex is less negative than the zeta potential of the double strand RNA alone; inserting the complex into an efferent or afferent mammalian vessel *in vivo* thereby increasing permeability of the vessels within the target tissue and delivering the double strand RNA to the cell, wherein the double strand RNA inhibits expression of the gene. Claims 13, 14, and 17 depend from claim 11 and include all the limitations of claim 11 with the further limitations wherein increasing the permeability of the vessel consists of increasing pressure against vessel walls; wherein the cell is selected from brain cells or skeletal muscle cells; wherein the complex has a positive charge; and wherein increasing the pressure consists of increasing volume of fluid within the vessel. It is noted that the instant specification does not define the term, "target tissue". Therefore, the Examiner is interpreting this term broadly to include any tissue, but more specifically the injection site.

Sioud et al. disclose the nuclease-resistant protein kinase C α ribozyme blocks glioma cell growth in rats (see Abstract). Specifically, Sioud et al. teach the inhibition of protein kinase C α gene expression following a single injection of cationic liposome ribozyme complexes into glioma tumors *in vivo* (see Figures 4 and 5). It is noted that Sioud et al. disclose that the cationic liposome ribozyme complexes were injected into

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the center of the glioma tumor, where the Examiner is interpreting the tumor to be the efferent target tissue; the site of injection represents the site of increased permeability since the needle used is external to the tumor tissue; the process of injecting would increase pressure and fluid against the vessel walls since the cationic liposome ribozyme complexes are themselves in an aqueous solution and represent the injection volume that would increase pressure against the vessel wall upon injection into the extravascular space.

It is further noted that Sioud et al. are silent regarding whether the zeta potential of the ribozyme complex is less negative than the zeta potential of the ribozyme alone. However, the burden of establishing whether the prior art cationic liposome ribozyme complex has the function of exhibiting zeta potential less negative than the zeta potential of the ribozyme alone, under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO

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can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product.” The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594, 596, (CCPA 1980), quoting *In re Best* 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the cationic liposome ribozyme complex disclosed by Sioud et al. would or would not have the additional functional limitation of exhibiting zeta potential less negative than the zeta potential of the ribozyme alone, as instantly claimed.

Therefore, absent evidence to the contrary, Sioud et al. anticipate claims 11, 13, 14, 15, and 17.

Claims 11, 13, 14, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Czubayko et al. (Proc. Natl. Acad. Sci., 1996 Vol. 93:14753-14758).

The claims are as described above in the 35 U.S.C. 102(b) as being anticipated by Sioud et al. It is noted that the instant specification does not define the term, “target tissue”. Therefore, the Examiner is interpreting this term broadly to include any tissue, but more specifically the injection site.

Czubayko et al. disclose metastasis is modulated by a ribozyme targeting secreted growth factor pleiotrophin in nude mice (see Abstract). Specifically, Czubayko et al. disclose human melanoma cells transfected with varying PTN-ribozyme constructs and lipofectamine and subsequently injected into subcutaneous sites on the flanks of athymic nude mice inhibit PTN gene expression (see Figure 2C). It is noted that Czubayko et al. disclose that the PTN-ribozyme constructs were injected into two

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subcutaneous sites on the flanks of mice, where the Examiner is interpreting the flanks to be the efferent target tissue; the site of injection represents the site of increased permeability since the needle used is external to the target tissue; the process of injecting would increase pressure and fluid against the vessel walls since the PTN-ribozyme constructs are themselves in an aqueous solution and represent the injection volume that would increase pressure against the vessel wall upon injection into the extravascular space.

It is further noted that Czubayko et al. are silent regarding whether the zeta potential of the PTN-ribozyme construct complex is less negative than the zeta potential of the ribozyme alone. However, the burden of establishing whether the prior art PTN-ribozyme construct complex has the function of exhibiting zeta potential less negative than the zeta potential of the ribozyme alone, under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO

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can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594, 596, (CCPA 1980), quoting *In re Best* 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the PTN-ribozyme construct complex disclosed by Czubayko et al. would or would not have the additional functional limitation of exhibiting zeta potential less negative than the zeta potential of the ribozyme alone, as instantly claimed.

Therefore, absent evidence to the contrary, Czubayko et al. anticipate claims 11, 13, 14, and 17.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11 and 13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmer, A. (Methods, 1999 Vol. 18:286-295, made of record in the previous Office Action mailed August 24, 2005) in view of Vaish et al. (Nucleic Acids Research, 1998 Vol. 26:5237-5242), and Zhang et al. (Human Gene Therapy, 1999 Vol. 10:1735-1737, made of record in the previous Office Action mailed August 24, 2005).

Claim 11 is drawn to a process for inhibiting the expression of a gene in a cell in a target tissue in a mammal comprising mixing a double stranded RNA and a polymer or non-viral vector to form a complex wherein the zeta potential of the complex is less negative than the zeta potential of the double strand RNA alone; inserting the complex into an efferent or afferent mammalian vessel *in vivo* thereby increasing permeability of the vessels within the target tissue and delivering the double strand RNA to the cell, wherein the double strand RNA inhibits expression of the gene. Claims 13-18 depend from claim 11 and include all the limitations of claim 11 with the further limitations, wherein increasing the permeability of the vessel consists of increasing pressure against vessel walls; wherein the cell is a liver cell; wherein the complex has a positive or negative charge; wherein increasing the pressure consists of increasing volume of fluid within the vessel; and wherein the solution is inserted within 2 minutes. It is noted that the instant specification does not define the term, "target tissue". Therefore, the Examiner is interpreting this term broadly to include any tissue, but more specifically the injection site.

Zimmer teach delivering an antisense oligonucleotide complexed with positive and negative charged polymers into a liver cell via tail vein injection (see Abstract).

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Specifically, Zimmer teach mixing an antisense and a polymer, wherein the zeta potential of the complex is less negative than the zeta potential of the antisense alone (see Table 2 and page 290, first full paragraph, which states, "at a lower ratio the surface charge of the nanoparticles is decreased by the ODNs as indicated by a decreased ζ potential"). Zimmer teach Protocol A, which provides cationically (positively) charged oligonucleotide-loaded nanoparticles and Protocol B, which provides anionically (negatively) oligonucleotide-loaded nanoparticles (see page 287, first and second paragraphs). It is noted that Zimmer et al. teach that the antisense nanoparticle complexes were injected into the tail vein, where the Examiner is interpreting the tail vein to be the efferent target tissue; the site of injection represents the site of increased permeability since the needle used is external to the target tissue; the process of injecting would increase pressure and fluid against the vessel walls since the antisense nanoparticle complexes are themselves in an aqueous solution (e.g. injection volume) that would increase pressure against the vessel wall upon injection into the extravascular space.

It is noted that Zimmer et al. are silent regarding whether or not the antisense oligonucleotide complexed with positive and negative charged polymers delivered into a liver cell via tail vein injection inhibited expression of a target gene. However, the burden of establishing whether the prior art antisense oligonucleotide complexed with positive and negative charged polymers has the function of inhibiting gene expression, under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or

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composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594, 596, (CCPA 1980), quoting *In re Best* 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the antisense oligonucleotide complexed with positive and negative charged polymers taught by Zimmer et al. would or would not have the additional functional limitation of inhibiting expression of a target gene, as instantly claimed.

Zimmer do not teach a double stranded RNA or inserting a dsRNA into a cell of a mammal within 2 minutes.

Vaish et al. teach that antisense oligonucleotides and ribozymes are two approaches that use similar techniques to achieve the same goal (see page 5239, first column). For example Vaish et al. teach, "The first step for inhibition of gene expression by a ribozyme is its binding to the mRNA. This step is akin to the antisense

oligodeoxynucleotide method (AS-ODN) used for the same purpose. It is, therefore, not surprising that both approaches benefit from experience in each others areas".

Zhang et al. teach that the tail vein injection of naked plasmid DNA enables foreign gene expression in the liver (see Abstract). Zhang et al. also teach maximal gene expression was achieved when the DNA solution was injected within 7-120 seconds (see Figure 1, injection speed). Zhang et al. conclude that the rapid injection of plasmid DNA has great potential for a wide variety of laboratory studies.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to devise a process for inhibiting the expression of a gene in a cell in a target tissue in a mammal using the methods taught by Zimmer et al.

One of ordinary skill in the art would have been motivated to devise a process for inhibiting the expression of a gene in a cell in a target tissue in a mammal for the purpose of nucleic acid therapy. One of ordinary skill in the art would have been motivated to substitute the antisense nucleic acid as taught by Zimmer with the dsRNA as instantly claimed since Vaish et al. teach a dsRNA would have been considered to be structurally equivalent to an antisense since both are sequence specific nucleic acid inhibitors of gene expression, which are used for the same purpose. Further, see MPEP 2144.06. It would have been obvious to one of ordinary skill in the art to insert the complex within 2 minutes since Zhang et al. taught maximal nucleic acid expression by tail vein injection is achieved when DNA solutions are injected within 7-120 seconds.

One would have had a reasonable expectation of success at devising a process for inhibiting the expression of a gene in a cell in a target tissue in a mammal because

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Zimmer clearly teach the successful delivery of an antisense nucleic acid to a liver cell and since antisense and dsRNA are both sequence specific nucleic acid inhibitors of gene expression and since antisense and dsRNA are art-recognized functional and structural equivalents, the instant invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

A handwritten signature in black ink, appearing to read "Tina C. Hill". The signature is fluid and cursive, with a horizontal line above the "Hill" portion.

tcg

July 20, 2006